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Adverse events following Measles-Mumps-Rubella and varicella immunization: A safety profile analysis and comparison of different vaccination schedules based on the Italian Pharmacovigilance Network in the Veneto Region

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ABSTRACT

Objective: The vaccines for measles, mumps, rubella and varicella (MMR and V) have been mandatory in Italy since 2017. Two different vaccination strategies are suggested for the first dose: trivalent MMR and a separate V vaccine or the tetravalent MMRV vaccine. Our aim is to compare the safety profile of MMRV and MMR-V vaccines through the passive adverse event reporting system in the Veneto region and to perform a case-by-case review of a few conditions of interest (febrile and afebrile seizures, ataxia, encephalitis, Guillain-Barré Syndrome, thrombocytopenia, neutropenia and Henoch-Schönlein Purpura). Age and sex differences were also explored.

Methods: We identified all reports following MMRV or MMR-V vaccination in the Veneto Region and received into the National Pharmacovigilance Network between 2007 and April 30, 2022.

Results: 9,510 reports were retrieved, of which 5,662 (59.5 %) were related to MMRV and 3,848 (40.5 %) to MMR-V. No safety signals were detected supporting the evidence that MMRV and MMR-V vaccinations have a good safety profile. The reporting rate (RR) for serious events between 2007 and 2022 resulted in 13.67 per 10,000 administered doses for MMRV and 10.90 for MMR-V.

Conclusion: Passive surveillance data show a significantly higher rate of serious events for males 0–2 years old, both overall and stratified per vaccination strategy. Further studies are needed to confirm this observation. The analyses suggest that retrieved differences do not have a significant impact on the overall safety of both formulations.

1. Background

In Italy the measles-mumps-rubella (MMR) vaccine has been recommended at a national level since the early 1990s, while universal varicella immunization began only with the 2014 birth cohort (Preventive National Vaccination Plan – PNPV 2005–2007). All 4 vaccines became mandatory nationwide starting from the 2017 birth cohort due to vaccination coverage worryingly dropping below 95 % (Law n. 119/2017). Indeed, vaccine hesitancy led to a decrease in measles vaccination uptake in recent years resulting in an alarming outbreak with over 4,000 cases and a few cases of death registered in Italy in 2017.

Currently, for the 4 vaccines, a two-dose schedule is recommended at 12 months and 5 years of age (PNPV 2023–2025). Two different vaccination strategies were initially suggested for the first dose: either the use of the tetravalent MMRV vaccine or trivalent MMR with a separate Varicella (V) shot administered in the same vaccination session.

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For the second dose, the preferred strategy is administering the tetravalent MMRV vaccine. The available combined MMRV was approved by Food and Drug Administration (FDA) and the European Medicines Agency (EMA) between 2005 and 2006. The tetravalent formulation offers several advantages including a decrease in the overall burden of injections, increased parental acceptance, and the potential for decreased local reactions, leading to higher vaccination compliance and improved immunization rates (Bauchau et al., 2015). Since the introduction of the tetravalent formulation, several post-marketing surveillance studies showed an approximately 2-fold increased risk of febrile convulsions for MMRV compared to MMR-V after the first dose (Leung et al., 2015; Ma et al., 2015a; Schink et al., 2014). Therefore, the MMR-V schedule was recommended for children at risk of febrile convulsions.

According to the Centers for Disease Control (CDC), the best strategy should be decided through a successful two-way discussion between healthcare providers and the parents/caregivers (CDC, 2021). The main aims of passive surveillance systems are to promptly detect new risks and enhance transparent communication on vaccine safety data to increase population confidence in immunization programs and their involvement in decisions regarding vaccination. Indeed, mandatory vaccination should be considered an emergency measure, while a culture of vaccination founded on trust should be actively promoted across all levels of the National Health System (NHS).

This study aims to assess and compare the safety profiles of MMRV and MMR-V vaccines over a large period through the passive adverse event reporting system (Italian Pharmacovigilance Network) in the Veneto region and to perform a detailed case-by-case review of a few conditions of interest identified from the literature. A secondary aim is to explore differences in the distribution of Adverse Events Following Immunization (AEFIs) by sex and age.

2. Materials and Methods

2.1. Data source and included reports

The Italian Pharmacovigilance Network (RNF) is the national surveillance system of AEFIs. It was established in 2001 and is managed by the Regional Pharmacovigilance Centers (RPCs) coordinated by the Italian Medicine Agency (AIFA). All AEFI reports from healthcare professionals, pharmacists, patients/citizens, and pharmaceutical companies are collected in the RNF and analyzed by AIFA in collaboration with the RPCs to detect potential safety signals.

Reports notified as "serious" are defined as "*any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect*" (Directive, 2010/84/EU). Moreover, clinicians can classify an event as serious if they judge it as clinically relevant. All serious reports are evaluated by the RPCs and AIFA to establish a possible causal relationship with vaccines (causality assessment) according to the algorithm developed by World Health Organization (WHO) (WHO User Manual – 2019 Update). A causal association is classified as "consistent" when the relationship between the AEFI and the vaccination is supported by robust evidence, "indeterminate" when evidence is too limited, "inconsistent" when evidence excludes a causal relationship or "unclassifiable" in case of inadequate or incomplete information.

Administered Doses (AD) were obtained from the Regional Vaccination Registry of the Veneto Region to calculate Reporting Rates (RR) (Supplementary file 1). The Veneto region accounts for almost 5,000,000 inhabitants, of which 102,329 are infants under 2 years old and 1,135,750 are children between 3 and 11 years old (Istat Data, 2021). In 2021, vaccination coverage for the first dose (at 24 months) of each MMRV vaccine was approximately 95 % for measles, mumps, and rubella and 94 % for varicella. Data for the second dose coverage (i.e., for vaccinations at age 5/6) were 88 % for measles, mumps, and rubella, and almost 84 % for varicella (Istat Data, 2021).

All AEFI reports following MMRV or MMR-V vaccination in the Veneto Region and received into the RNF up to April 30th, 2022, were included. MMR-V reports were identified by searching those referring to MMR and V vaccines administered in the same session.

These data also include reports from an active surveillance project on the safety profile of MMRV and MMR-V first doses in the Veneto Region, conducted from 08/01/2013 to 07/31/2014 (Cocchio et al., 2015). Anonymized MMRV and co-administered MMR and V AD between 01/01/2007 and 04/30/2022 categorized into sex, age group and year of administration were included.

The study met the university's guidelines for protecting human subjects concerning safety and privacy. The analysis of spontaneous reporting data doesn't need ethical approval according to local laws and regulations.

2.2. Data collection and data analysis

All reported AEFIs were described according to distribution by vaccination strategy, sex and age groups (infants, children, adolescents, adults). Sex was defined according to the Sex and Gender Equity in Research (SAGER) guidelines, i.e. as "*a set of biological attributes that are associated with physical and physiological features*" (Van Epps et al., 2022). Serious reports' distribution by vaccine strategy and seriousness criteria was also described. Moreover, distribution by IME (Important Medical Events, a list of potential AEFI judged important by EMA) was analyzed to explore possible differences in clinically relevant events between the two vaccine formulations. RRs for AD were calculated for MMRV and MMR-V both overall and for serious reports between 2007 and the first four-month period of 2022.

The safety profile of the two vaccination strategies was described according to a few conditions of interest identified by literature as related or potentially related to MMRV or MMR-V vaccines and, therefore, potentially influencing trust in vaccination. Specifically: febrile and afebrile seizures, ataxia, encephalitis, Guillain-Barré Syndrome, thrombocytopenia, neutropenia and Henoch-Schönlein Purpura (Bauchau et al., 2015; Cecinati et al., 2013; Muturi-Kioi et al., 2016; Pahud et al., 2012; Patja et al., 2001; Piram et al., 2018; Plesner et al., 2000; Watson et al., 2012).

In the RNF, the AEFIs are coded using the Medical Dictionary for Regulation Activities (MedDRA). The reports describing the conditions of interest were identified using a search strategy based on Standardized MedDRA Queries (SMQ), when available. Otherwise, a list of Preferred Terms (PTs) was selected for each condition according to specific diagnostic criteria. Searching strategies and case definition criteria are described in Supplementary file 2. The team assessed each report to identify the diagnostic certainty level of the event and to classify the causal relationship with vaccination. Specifically, retrieved reports for each condition were ranked according to Brighton Collaboration case definition criteria (when available) to exclude "level 5" ones (i.e., "not a case"). Only reports "consistent" or "indeterminate" at causality assessment were included for further analyses. The date of onset for each condition was obtained by analyzing available documentation (case description, discharge letter, etc.); the time of onset for each report was then calculated considering the time frame between the vaccination date and the date of onset. The time of onset for each condition was calculated as median and interquartile range. RR per AD for consistent and indeterminate cases referred to the conditions of interest for each vaccination schedule was calculated.

Regarding the secondary aim, RR per AD by sex and age class (i.e. 0–2 vs 3–12) was explored.

Differences in the frequency distribution (RR) were tested using Chi-square tests. The significance level was set at 0.05.

3. Results

A total of 9,510 AEFI reports were obtained. Of these, 5,662 reports

(59.5 %) and 3,848 (40.5 %) were MMRV and MMR-V related, respectively.

In the overall sample, 9,162 (96.34 %) reports concerned infants (i.e., from 28 days to less than 24 months; 94.51 % for MMRV and 99.04 % for MMR-V) and 323 (3.39 %) referred to children (i.e., from 2 to less than 12 years; 5.28 % for MMRV and 0.62 % for MMR-V). Table 1 shows the distribution of reports by sex and vaccine group.

RR in the period between 2007 and 2022 for MMRV resulted of 69.07 per 10,000 CE, meanwhile for MMR-V was 112.26 ($p < 0.001$).

Ninety-eight percent (98.3 %) of the total reports showed either a complete resolution of the AEFI or an improvement.

Serious reports were 1,491/9510 (15.7 %), specifically 1,116/5662 (19.7 %) for MMRV and 375/3848 (9.7 %) for MMR-V. The proportion of males was 55.6 % (55.25 % for MMRV and 56.60 % for MMR-V).

Table 2 shows the distribution of serious AEFIs according to seriousness criteria and vaccination approach.

Reports with persistent/significant disability referred to autism/developmental disorders (N = 4) and Type 1 diabetes (N = 1). All these conditions resulted as inconsistent with vaccination. Both life-threatening reports referred to thrombocytopenia and were judged as indeterminate and consistent, respectively. These cases were described as improved at follow-up.

RR for serious events between 2007 and 2022 resulted in 12,86 per 10,000 AD (1,484/1,154,313); respectively 13.67 per 10,000 AD (1,113/813,956) for MMRV and 10.90 (371/340,357) for MMR-V ($p < 0.001$).

A total of 2170 reports with at least one PT IME was retrieved (22.82 % of all reports). The most reported IME was *"Hyperpyrexia"* accounting for 92.1 % of all retrieved IME (respectively 91,2% for MMRV and 94.4 % for MMR-V).

Table 3 describes main characteristics of retrieved reports for considered conditions of interest resulted either consistent or indeterminate at causality assessment.

The case selection strategy is described in Supplementary file 3. Table 4 compares RR for MMRV and MMR-V consistent or indeterminate cases for each condition of interest.

Regarding the secondary aim, no significant differences between sex and/or age class were found among all AEFIs (RR per 10,000 CE respectively 82.42 for males and 81.15 for females with a reporting rate ratio of 1,01). Distribution of serious AEFIs resulted significantly higher for males compared to females (RR 13.93 vs 11.72 per 10,000 CE, $p < 0.001$, RR ratio 1.19) and age class 0–2 (related to the first dose) compared to 3–12 (RR 31.82 vs 1.18 per 10,000 CE, $p < 0.001$, RR ratio 26.96). Significant differences between sexes were also retrieved stratifying by age class and vaccine type, with RR for serious AEFIs significantly higher for males 0–2 years old receiving MMRV compared with females of the same age class and vaccine type (RR 29.73 vs 25.57 per 10,000 CE, $p < 0.05$, male:female RR ratio 1.16). A significant statistical difference was also observed comparing males 0–2 years old receiving MMR-V with females of the same age class and vaccine type (RR 12.53 vs 10.19 per 10,000 CE, $p = 0.049$, male:female RR ratio 1.23).

Among the condition of interest, sex differences were analyzed for febrile convulsions and thrombocytopenia: no significant differences were retrieved, neither considering both formulations nor stratifying per vaccine type. However, RR for febrile convulsions following the MMRV vaccine showed a trend to significance ($p = 0.07$, male:female RR ratio = 1.36) when compared with the MMR-V schedule.

Table 1
Distribution of reports by sex and vaccine group in the Veneto Region during the study period (2007–2022).

	MMRV		MMR-V		TOT	
	N	%	N	%	N	%
MALE	2965	52.37	1934	50.26	4899	51.51
FEMALE	2678	47.30	1906	49.53	4584	48.20
UNKNOWN	19	0.34	8	0.21	27	0.28
TOTAL	5662		3848		9510	

Table 2
Distribution of serious events by seriousness criteria and vaccine group in the Veneto Region during the study period (2007–2022). (Other important medical events: When the event does not align with the other outcomes but still poses a risk to the patient, potentially necessitating medical or surgical intervention to prevent any of the other outcomes).

	MMRV		MMR-V		TOT	
	N	%	N	%	N	%
OTHER IMPORTANT MEDICAL EVENTS	957	85.7	339	90.4	1,296	87
HOSPITALIZATION / PROLONGED HOSPITALIZATION	152	13.6	36	9.6	188	13
PERSISTENT / SIGNIFICANT DISABILITY	5	0.4	–	–	5	0.3
LIFE THREATENING CONDITIONS	2	0.2	–	–	2	0.1
DEATH	–	–	–	–	–	–

4. Discussion

Between 2007 and 2022, a high number of AEFI reports was collected, allowing an analysis of a significant amount of data. Overall, RR was higher compared to other passive surveillance studies conducted on the same vaccines (Pan et al., 2021). On the other hand, the proportion of serious reports was similar (between 10 % and 15 %) (Clothier et al., 2017). Despite underreporting being a well-known bias of passive surveillance studies, the high RR detected in our study supports the effective performance of the Italian passive surveillance system at regional level. Similar proportions in the distribution of reports between sexes were detected, as retrieved in comparable studies (Clothier et al., 2017).

As expected, almost all the reports regarded infants and children. It is worth noting that surveillance data from the first dose, covering 98 % of the received reports, reached high coverage rates (almost 95 %), ensuring potential comprehensive vaccine safety monitoring.

Overall results support the evidence that MMRV and MMR-V vaccinations have a good safety profile. Indeed, no signals were detected during the study period, and all identified AEFIs were expected according to the vaccines' fact sheet. Moreover, follow-up data showed a positive outcome for the retrieved AEFIs. The only two life-threatening cases potentially related to vaccination referred to thrombocytopenia, a rare adverse event already detected in pre-clinical studies. Furthermore, both cases resulted improved at the time of reporting. No cases of death were retrieved. Finally, all cases with persistent disability were not consistent at causality assessment and mostly (4 out of 5) described autism and developmental disorders. Several studies have provided no support for an association between vaccinations and neurodevelopmental or autism spectrum disorders (Taylor et al., 2014). In 2019, a nationwide cohort study conducted in Denmark on 657,461 children strongly supported the absence of an increased risk for autism following MMR vaccination (Hviid et al., 2019). Despite the evidence collected, cases of autism or developmental disorders have been reported even in the last few years. This confirms the difficulty in conveying scientific evidence to the public, while misleading information is more easily accessible.

Our study shows a higher overall RR for MMR-V compared to MMRV. However, RR for serious events resulted significantly higher for MMRV.

Supporting this result, an actual higher reactogenicity of MMRV formulation has been shown in different studies in the literature. Two metanalysis conducted to compare the immunogenicity and reactogenicity of the two MMRV and MMR-V formulations found an increased incidence of fever and rash following MMRV administration (Ma et al., 2015a; Leung et al., 2015). The same result was found in an active surveillance study conducted in Italy between 2013 and 2014

Table 3
Characteristics of consistent or indeterminate reports describing conditions of specific interest retrieved during the study period (2007–2022).

CONDITIONS	N	AGE N (%)	SEX N (%)	VACCINE N (%)	DIAGNOSTIC CERTAINTY N (%)	TIME OF ONSET* (days)	OUTCOME N (%)	FREQUENCY OF OCCURENCY (ACCORDING TO DATA SHEET)
FEBRILE CONVULSIONS	184	1 year old = 181 (98.4) 2 years old = 2 (1.1) 4 years old = 1 (0.5)	M = 101 (54.9) F = 82 (44.6) unknown = 1 (0.54)	MMRV = 146 (79.3) MMR-V = 38 (20.6)	1 = 54 (29.3) 2 = 9 (4.9) 3 = 9 (4.9) 4 = 112 (60.9)	median = 8 quartiles = 7–9	complete resolution = 173 (94.02) improvement = 2 (1.1) sequelae = 2 (1.1) not available = 8 (4.3)	Not frequent (≥1/1,000, < 1/100)
AFEBRILE SEIZURES	7	1 year old = 7	M = 4 (57.1) F = 3 (42.8)	MMRV = 5 (71.4) MMR-V = 2 (28.6)	1 = 4 (57.1) 4 = 3 (42.8)	Median = 7 quartiles = 5–10	complete resolution = 5 (71.43)	Not known
ATAXIA	10	1 year old = 8 (80) 2 year old = 2 (20)	M = 7 (70) F = 3 (30)	MMRV = 7 (70) MMR-V = 3 (30)	not applicable	median = 5 quartiles = 3–10	complete resolution = 7 (70) improvement = 1 (10) not yet recovered = 1 (10) not available = 1 (10)	Rare (≥1/10,000, < 1/1,000)
ENCEPHALITIS	4	1 year old = 3 (75) 2 years old = 1 (25)	M = 3 (75) F = 1 (25)	MMRV = 4	1 = 2 (50) 2 = 1 (25) 4 = 1 (25)	median = 7.2 quartiles = 4–10.25	complete resolution = 3 (75) not available = 1 (25)	Not known (observed in severe immunocompromised)
GUILLAIN-BARRE SYNDROME	1	6 years old	M	MMRV	1	14	complete resolution	Not known
THROMBOCYTOPENIA	20	1 year old = 19 (95) 5 years old = 1 (5)	M = 11 (55) F = 9 (45)	MMRV = 18 (90) MMR-V = 2 (10)	1 = 18 (90) 4 = 2 (10)	median = 18 quartiles = 14–7.5	complete resolution = 13 (65) improvement = 6 (30) not yet recovered = 1 (5)	Not known
NEUTROPENIA	2	1 year old = 2	M = 1 (50) F = 1 (50)	MMRV = 2	1 = 1 (50) 4 = 1 (50)	median = 5.5	complete resolution = 1 (50) not available = 1 (50)	Not reported
HENOCH-SCHONLEIN PURPURA	1	1 year old	F	MMR-V	2	15	complete resolution	Rare (≥1/10,000, < 1/1,000)

*Systemic adverse reactions following live vaccines may occur after the first 72 h from injection (time window 3–21 days).

Table 4
Reporting Rate of MMRV and MMR-V (consistent or indeterminate cases) for included conditions of specific interest calculated over the entire study period (2007–2022).

CONDITIONS	MMRV RR (per 10,000 CE)	MMR-V RR (per 10,000 CE)	SIGNIFICANCE
FEBRILE SEIZURES	1.79	1.08	**p < 0.01**
AFEBRILE SEIZURES	0.086	0.058	Not significant
ATAXIA	0.086	0.086	Not significant
THROMBOCYTOPENIA	0.22	0.05	p = 0.056
HENOCH-SCHONLEIN PURPURA	–	0.03	–
ENCEPHALITIS	0.049	–	–
NEUTROPENIA	0.024	–	–
GUILLAIN-BARRÉ SYNDROME	0.01	–	–

(Cocchio et al., 2015). The higher incidence of fever observed for MMRV may lead to a potentially higher incidence of febrile convulsions, as reported in the literature (Cocchio et al., 2015; Ma et al., 2015b; MacDonald et al., 2014; Schink et al., 2014). Several cohort studies have evidenced a higher risk of febrile convulsions following MMRV immunization, especially seven to ten days after vaccination (MacDonald et al., 2014; Klein et al., 2012). A cohort study estimated a two-fold higher significant risk (2.20, 95 % CI 1.04–4.65) for MMRV vs MMR-V in a 5–12-day period (Jacobsen et al., 2009). Also, results from our study evidenced a significantly higher rate of febrile convulsions for MMRV compared to MMR-V (1.79 vs 1.09 per 10,000 CE). According to our data, the median time of occurrence of post-vaccination febrile seizures was 8 days, with a difference between the two immunization strategies. The interquartile range of the time of onset for MMRV was between 7 and 9 days and showed a peak 6–8 days after the injection, while MMR-V cases were distributed along an interquartile range between 5 and 10 days. Moreover, no sequelae were observed, and most cases were completely solved at follow-up, supporting the good prognosis of these events.

A few cases of seizures resulted as not related to fever, with a similar proportion between the two schedule types. It's possible that at least some of these events were related to fever, but body temperature was not recorded. However, follow-up for these cases was limited to the resolution of the event and therefore it cannot be excluded that some of them were only later diagnosed with epilepsy or other neurological disorders. According to the literature, immunization is safe also for children with epilepsy and seizures and they are not associated with any sequelae or adverse outcomes (Klein et al., 2012). All cases were completely recovered at follow-up.

Regarding gait disorders, published passive surveillance data reported a few cases occurred in a plausible time window after immunization (Plesner et al., 2000). However, a large retrospective epidemiological study conducted over a 6-year period, retrieved no association with MMR vaccination (Miller et al., 2005). Indeed, a recent cohort study conducted on the US Vaccine Safety Datalink showed no risk difference in ataxia occurrence between MMRV and MMR-V either considering a focal (14–28 days) or broad (0–42 days) risk interval after immunization (Klein aet al., 2015). Consistently, in our study no statistically significant differences between RR among the two strategies were observed. A post-marketing surveillance study conducted in the US (Sharrar et al., 2000) estimated an incidence of ataxia following

varicella vaccination of 0.15 cases every 100,000 CE. We observed a similar RR. These rates are much lower than the ones following infection (5/100,000) (van der Maas et al., 2009).

Several epidemiological studies investigated the risk of encephalitis following MMR vaccination and found no causal correlation (Mäkelä et al., 2002; Pahud et al., 2012; Ray et al., 2006; Ward et al., 2007). In the literature there is no evidence of a differential risk between the two schedules (Klein et al., 2015). All our cases of encephalitis followed MMRV and were improved or completely recovered at follow-up.

In our study, we found only one case of GBS, which was likely related to EBV concomitant infection. In any case, the literature does not provide any evidence of a possible causal relationship with MMRV/MMR-V vaccination (Demicheli et al., 2012; Patja et al., 2001).

The risk of developing idiopathic thrombocytopenic purpura (ITP) following MMRV or MMR-V vaccinations has been documented in several studies (Bertuola et al., 2010; Black et al., 2003; Klein et al., 2015). The physio-pathological mechanism may depend on cross-reactive autoantibodies against antigens naturally present on platelets (Cecinati et al., 2013). In children the estimated relative risk of developing ITP in the six weeks following vaccination was found to be between 2.14 and 6.3 (Bertuola et al., 2010; Black et al., 2003; Cecinati et al., 2013; Miller et al., 2001). According to a systematic review, the incidence rate of ITP following MMRV/MMR-V vaccinations is 2.6/100,000 vaccine doses (range 0.09–4) (Mantadakis et al., 2010), much lower than the background rate of ITP in children aged 1–7 years old (10.5/100,000) (Wormsbecker et al., 2019) and the incidence rate of ITP following natural measles (33/100,000) and rubella infections (between 6 and 1,200/100,000) (Mantadakis et al., 2010). Furthermore, ITP following immunization is described as less serious, with mild symptoms such as bruising and petechiae and no lasting effects, whereas ITP following viral infections chronicizes in 25–28 % of cases (Cecinati et al., 2013). Our results show similar RR and all cases showed improvement or were completely solved at follow-up. The risk–benefit profile is such that the American Society of Hematology recommends MMR vaccination in unimmunized children with a history of ITP (Harris et al., 2017). According to our study, RR for MMRV resulted higher than MMR-V with a trend towards significance ($p = 0.056$) but this evidence was not confirmed in the literature (Klein et al., 2015).

According to the literature, also neutropenia is not uncommon following live vaccine administration (Muturi-Kioi et al., 2016). An Italian case report described two cases of transient neutropenia following MMRV immunization that occurred in one-year-old children (Giannotta, 2018). According to our study only two cases were found; one case had recovered at follow-up, while the other one had no follow-up available.

Schönlein-Henoch Purpura (HSP) is the most common vasculitis in childhood, with an estimated incidence of 6.2 cases for 100,000 children per year (Watson et al., 2012). A much lower rate was found after MMR immunization during an active surveillance study following a two-year mass vaccination campaign (2.14/1,000,000 CE) (Shu et al., 2011). In our passive surveillance study, only one case was retrieved, and a favorable prognosis was found. According to the literature, the causal association between immunization and HSP is still uncertain. A case cross-over study comparing the exposure to MMR vaccination of 167 children suffering from HSP found no significant association (OR 1.6, 95 % CI 0.8–3) (Piram et al., 2018). On the other hand, a case-control study conducted in Italy on 288 cases and 617 controls estimated an increased risk of HSP after vaccination (OR 3.4; 95 % CI 1.2–10) (Da Dalt et al., 2016).

Regarding the analysis of possible sex differences, our results showed a significantly higher rate of serious events for males 0–2 years old, both overall and stratified per vaccination strategy. However, the RR ratio resulted in limited clinical relevance with an increased risk between 16 % and 23 %. This difference is not related to a reporting bias since no differences were observed among overall reported AEFIs between males and females. Indeed, other authors found higher RR for adult females, while no differences were observed for infant and childhood vaccines (Neunert et al., 2019). According to our data, the observed difference does not involve either febrile convulsions or thrombocytopenia. Literature regarding sex differences in vaccine safety profiles is scarce. To explore this issue, a systematic review conducted in 2014 retrieved only 3 studies that referred to MMR(V) (two RCTs and 1 cohort study) (Weber & Schlagenhauf, 2014). The authors concluded that the only retrieved difference regarded the incidence of arthralgia, which resulted higher in adolescent females compared to males. A self-Controlled Case Series (SCCS) study using Vaccine Safety Datalink identified a higher incident rate ratio of immune thrombocytopenia following MMR for males compared to females (14,59 vs 3,22). Although our data retrieved a higher RR for thrombocytopenia for males compared to females, this evidence was not significant.

4.1. Strengths and limitations

The RNF, a spontaneous reporting system, faces limitations like underreporting, incomplete information, and difficulty establishing precise vaccine-AEFI causality. Despite biases, passive surveillance acts as an early warning system, utilizing extensive data. This aided safety profile exploration for measles-mumps-rubella and varicella vaccines, including rare events. The availability of administered doses enabled reliable RR comparisons. Analyzing reports by specific conditions identified serious cases linked or potentially related to immunization.

5. Conclusion

The increase in mandatory vaccines has affected the population's confidence in immunization. This led to the need to develop strategies to counteract a dangerous distrust. A key role is played by vaccine vigilance which needs to strengthen its activities to produce detailed safety data that can be transparently communicated. The present study analyzed a great number of reports confirming the safety of both MMRV and MMR-V schedules. Indeed, even if, according to literature, the causal role of vaccinations still needs to be established for a few of the conditions of interest, these events emerged as extremely rare, not affecting the risk–benefit ratio. Furthermore, despite MMRV appeared to be slightly more frequently associated with AEFI than MMR-V, at least about the serious AEFI, the retrieved difference is minimal and does not affect the advantages of single versus double injection of MMR-V.

6. Declaration of Generative AI and AI assisted technologies in the writing process

During the preparation of this work the author(s) used ChatGPT in order to improve readability and language. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

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CRediT authorship contribution statement

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Methodology, Data curation, Conceptualization. **Giovanna Zanoni:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Conceptualization. **Francesca Moretti:** Writing – review & editing, Resources, Project administration, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pmedr.2024.102711.

References

Bauchau, V., Van Holle, L., Cohen, C., 2015. Modelling hospitalisation ratios for febrile convulsions nd severe Varicella under combined measles, mumps, rubella, and Varicella (MMRV—Priorix-TetraTM) Compared to Separate MMR - V vaccination. Drug Saf. 38, 1095–1102. https://doi.org/10.1007/s40264-015-0326-4.

Bertuola, F., Morando, C., Menniti-Ippolito, F., Da Cas, R., Capuano, A., Perilongo, G., Da Dalt, L., 2010. Association between drug and vaccine use and acute immune thrombocytopenia in childhood. Drug-Safety. 33, 65–72. https://doi.org/10.2165/11530350-000000000-00000.

Black, C., Kaye, J.A., Jick, H., 2003. MMR vaccine and idiopathic thrombocytopaenic purpura. Br J Clin Pharmacol. 55, 107–111. https://doi.org/10.1046/j.1365-2125.2003.01790.x.

CDC (Centers for Disease Control and Prevention). MMR & Varicella Vaccines or MMRV Vaccine: Discussing Options with Parents. Page last reviewed: January 26, 2021. https://www.cdc.gov/vaccines/vpd/mmr/hcp/vacopt-factsheet-hcp.html. (accessed 26 June 2023).

Cecinati, V., Principi, N., Brescia, L., Giordano, P., Esposito, S., 2013. Vaccine administration and the development of immune thrombocytopenic purpura in children. Hum Vaccin Immunother. 9, 1158–1162. https://doi.org/10.4161/hv.23601.

Clothier, H.J., Crawford, N.W., Russell, M., Kelly, H., Buttery, J.P., 2017. Evaluation of "SAEFVIC", a Pharmacovigilance surveillance scheme for the spontaneous reporting of adverse events following immunisation in Victoria. Australia. Drug Saf 40, 483–495. https://doi.org/10.1007/s40264-017-0520-7.

Cocchio, S., Zanoni, G., Opri, R., Russo, F., Baldo, V., 2015. A postmarket safety comparison of 2 vaccination strategies for measles, mumps, rubella and varicella in Italy. Hum Vaccin Immunother 12, 651–654. https://doi.org/10.1080/21645515.2015.1101198.

Da Dalt L, Zerbinati C, Strafella MS, Renna S, Riceputi L, Di Pietro P, Barabino P, Scanferla S, Raucci U, Mores N, Compagnone A, Da Cas R, Menniti-Ippolito F; Italian Multicenter Study Group for Drug and Vaccine Safety in Children, 2016. Henoch-Schönlein purpura and drug and vaccine use in childhood: a case-control study. Ital J Pediatr. 42(1):60. https://doi.org/10.1186/s13052-016-0267-2.

Demicheli V, Rivetti A, Debalini MG, Di Pietrantonj C, 2012. Vaccines for measles, mumps and rubella in children. Cochrane Database Syst Rev 2012;2012:CD004407. https://doi.org/10.1002/14651858.CD004407.pub3.

Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human useText with EEA relevance n.d.:26.

Giannotta, G., 2018. MMRV vaccine associated transient neutropenia: description of two cases. J Clin Case Rep. 08 https://doi.org/10.4172/2165-7920.10001069.

Harris, T., Nair, J., Fediurek, J., Deeks, S.L., 2017. Assessment of sex-specific differences in adverse events following immunization reporting in Ontario, 2012–15. Vaccine. 35, 2600–2604. https://doi.org/10.1016/j.vaccine.2017.03.035.

Hviid, A., Hansen, J.V., Frisch, M., Melbye, M., 2019. Measles, mumps, rubella vaccination and autism. Ann Intern Med. 170, 513–520. https://doi.org/10.7326/M18-2101.

IstatData. Banca dati dell'Istituto Nazionale di Statistica. Available at: https://esploradati.istat.it/databrowser/#/it/dw/categories.

Jacobsen, S.J., Ackerson, B.K., Sy, L.S., Tran, T.N., Jones, T.L., Yao, J.F., Xie, F., Cheetham, T.C., Saddier, P., 2009. Observational safety study of febrile convulsion following first dose MMRV vaccination in a managed care setting. Vaccine. 27 (34), 4656–4661. https://doi.org/10.1016/j.vaccine.2009.05.056.

Klein, N.P., Lewis, E., Baxter, R., Weintraub, E., Glanz, J., Naleway, A., Jackson, L.A., Nordin, J.D., Lieu, T., Belongia, E.A., Fireman, B., 2012. Measles-containing vaccines and febrile seizures in children age 4 to 6 years. Pediatrics. 129, 809–814. https://doi.org/10.1542/peds.2011-3198.

Klein, N.P., Lewis, E., Fireman, B., Hambidge, S.J., Naleway, A., Nelson, J.C., Belongia, E. A., Yih, W.K., Nordin, J.D., Hechter, R.C., Weintraub, E., Baxter, R., 2015. Safety of measles-containing vaccines in 1-Year-old children. Pediatrics. 135, e321–e329. https://doi.org/10.1542/peds.2014-1822.

Law N. 119/2017, 31th July https://www.gazzettaufficiale.it/eli/id/2017/06/07/17G00095/sg (accessed February 8, 2023).

Leung, J.H., Hirai, H.W., Tsoi, K.K., 2015. Immunogenicity and reactogenicity of tetravalent vaccine for measles, mumps, rubella and varicella (MMRV) in healthy children: a meta-analysis of randomized controlled trials. Expert Review of Vaccines. 14, 1149–1157. https://doi.org/10.1586/14760584.2015.1057572.

Ma, S.-J., Li, X., Xiong, Y.-Q., Yao, A., ling Chen, Q., 2015a. Combination measles-mumps-rubella-Varicella vaccine in healthy children. Medicine (baltimore). 94, e1721.

Ma, S.-J., Xiong, Y.-Q., Jiang, L.-N., Chen, Q., 2015b. Risk of febrile seizure after measles–mumps–rubella–varicella vaccine: a systematic review and meta-analysis. Vaccine. 33, 3636–3649. https://doi.org/10.1016/j.vaccine.2015.06.009.

MacDonald, S.E., Dover, D.C., Simmonds, K.A., Svenson, L.W., 2014. Risk of febrile seizures after first dose of measles–mumps–rubella–varicella vaccine: a population-based cohort study. CMAJ. 186, 824–829. https://doi.org/10.1503/cmaj.140078.

Mäkelä, A., Nuorti, J.P., Peltola, H., 2002. Neurologic Disorders after measles-mumps-rubella vaccination. Pediatrics. 110, 957–963. https://doi.org/10.1542/peds.110.5.957.

Mantadakis, E., Farmaki, E., Buchanan, G.R., 2010. Thrombocytopenic purpura after measles-mumps-rubella vaccination: a systematic review of the literature and guidance for Management. J. Pediatrics 156, 623–628. https://doi.org/10.1016/j.jpeds.2009.10.015.

Miller, E., Waight, P., Farrington, C.P., Andrews, N., Stowe, J., Taylor, B., 2001. Idiopathic thrombocytopenic purpura and MMR vaccine. Arch. Dis. Childhood. 84, 227–229. https://doi.org/10.1136/adc.84.3.227.

Miller, E., Andrews, N., Grant, A., Stowe, J., Taylor, B., 2005. No evidence of an association between MMR vaccine and gait disturbance. Arch Dis Child. 90, 292–296. https://doi.org/10.1136/adc.2003.048165.

Muturi-Kioi, V., Lewis, D., Launay, O., Leroux-Roels, G., Anemona, A., Loulergue, P., Bodinham, C.L., Aerssens, A., Groth, N., Saul, A., Podda, A., 2016. Neutropenia as an adverse event following vaccination: results from randomized clinical trials in healthy adults and systematic review. PLoS One. 11, e0157385.

Neunert, C., Terrell, D.R., Arnold, D.M., Buchanan, G., Cines, D.B., Cooper, N., Cuker, A., Despotovic, J.M., George, J.N., Grace, R.F., Kühne, T., Kuter, D.J., Lim, W., McCrae, K.R., Pruitt, B., Shimanek, H., Vesely, S.K., 2019. American Society of Hematology 2019 guidelines for immune thrombocytopenia. Blood Adv. 3, 3829–3866. https://doi.org/10.1182/bloodadvances.2019000966.

Pahud, B.A., Rowhani-Rahbar, A., Glaser, C., Gavali, S., Salibay, C.J., Fireman, B., Dekker, C.L., 2012. Lack of association between childhood immunizations and encephalitis in California, 1998–2008. Vaccine. 30, 247–253. https://doi.org/10.1016/j.vaccine.2011.10.104.

Pan, X., Lv, H., Chen, F., Wang, Y., Liang, H., Shen, L., Chen, Y., 2021. Analysis of adverse events following immunization in Zhejiang, China, 2019: a retrospective cross-sectional study based on the passive surveillance system. Hum Vaccin Immunother. 17, 3823–3830. https://doi.org/10.1080/21645515.2021.1939621.

Patja, A., Paunio, M., Kinnunen, E., Junttila, O., Hovi, T., Peltola, H., 2001. Risk of guillain-Barré syndrome after measles-mumps-rubella vaccination. The Journal of Pediatrics. 138, 250–254. https://doi.org/10.1067/mpd.2001.111165.

Piram, M., Gonzalez Chiappe, S., Madhi, F., Ulinski, T., Mahr, A., 2018. Vaccination and risk of childhood IgA Vasculitis. Pediatrics. 142, e20180841.

National Vaccine Prevention Plan, PNPV 2023-2025 20/03/2023 https://www.quotidianosanita.it/allegati/allegato1679488094.pdf (accessed May 09, 2023).

Plesner, A.-M., Hansen, F.J., Taudorf, K., Nielsen, L.H., Larsen, C.B., Pedersen, E., 2000. Gait disturbance interpreted as cerebellar ataxia after MMR vaccination at 15 months of age: a follow-up study. Acta Paediatrica. 89, 58–63. https://doi.org/10.1111/j.1651-2227.2000.tb01188.x.

Ray, P., Hayward, J., Michelson, D., Lewis, E., Schwalbe, J., Black, S., Shinefield, H., Marcy, M., Huff, K., Ward, J., Mullooly, J., Chen, R., Davis, R., 2006. Encephalopathy after whole-cell pertussis or measles vaccination: lack of evidence for a causal Association in a Retrospective Case-Control Study. The Pediatric Infectious Disease Journal. 25, 768–773. https://doi.org/10.1097/01.inf.0000234067.84848.e1.

Schink, T., Holstiege, J., Kowalzik, F., Zepp, F., Garbe, E., 2014. Risk of febrile convulsions after MMRV vaccination in comparison to MMR or MMR-V vaccination. Vaccine. 32, 645–650. https://doi.org/10.1016/j.vaccine.2013.12.011.

Sharrar, R.G., LaRussa, P., Galea, S.A., Steinberg, S.P., Sweet, A.R., Keatley, R.M., Wells, M.E., Stephenson, W.P., Gershon, A.A., 2000. The postmarketing safety profile of varicella vaccine. Vaccine. 19, 916–923. https://doi.org/10.1016/S0264-410X(00)00297-8.

Shu, M., Liu, Q., Wang, J., Ao, R., Yang, C., Fang, G., Wan, C., Guo, W., 2011. Measles vaccine adverse events reported in the mass vaccination campaign of Sichuan province, China from 2007 to 2008. Vaccine. 29, 3507–3510. https://doi.org/10.1016/j.vaccine.2009.10.106.

Taylor, L.E., Swerdfeger, A.L., Eslick, G.D., 2014. Vaccines are not associated with autism: an evidence-based meta-analysis of case-control and cohort studies. Vaccine. 32, 3623–3629. https://doi.org/10.1016/j.vaccine.2014.04.085.

van der Maas, N.A.T., Bondt, P.E.V., de Melker, H., Kemmeren, J.M., 2009. Acute cerebellar ataxia in the Netherlands: a study on the association with vaccinations and varicella zoster infection. Vaccine. 27, 1970–1973. https://doi.org/10.1016/j.vaccine.2009.01.019.

Van Epps, H., Astudillo, O., Del Pozo, M.Y., Marsh, J., 2022. The sex and gender equity in Research (SAGER) guidelines: implementation and checklist development. European Science Editing. 48, e86910.

Ward, K.N., Bryant, N.J., Andrews, N.J., Bowley, J.S., Ohrling, A., Verity, C.M., Ross, E. M., Miller, E., 2007. Risk of serious neurologic disease after immunization of young children in Britain and Ireland. Pediatrics. 120, 314–321. https://doi.org/10.1542/peds.2006-3743.

Watson, L., Richardson, A.R.W., Holt, R.C.L., Jones, C.A., Beresford, M.W., 2012. Henoch schönlein purpura – a 5-Year review and proposed pathway. PLoS One. 7, e29512.

Weber, S.K., Schlagenhauf, P., 2014. Childhood vaccination associated adverse events by sex: a literature review. Travel Medicine and Infectious Disease. 12, 459–480. https://doi.org/10.1016/j.tmaid.2014.01.008.

WHO, Causality assessment of an adverse event following immunization (AEFI): user manual for the revised WHO classification, 2nd ed., 2019 update, ISBN: 9789241516990 (electronic version) (https://www.who.int/publications-detail-redirect/9789241516990, last accessed November 14, 2022).

Wormsbecker, A.E., Johnson, C., Bourns, L., Harris, T., Crowcroft, N.S., Deeks, S.L., 2019. Demonstration of background rates of three conditions of interest for vaccine safety surveillance. PLoS One. 14, e0210833.